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ANNUAL PROGRESS REPORT AND FINAL TECHNICAL REPORT

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Harvey J. Karten, M.D.

Washington School of Psychiatry

ANATOMICAL STUDY OF HIPPOCAMPAL DISCHARGE PATHWAYS AND CURRENT  
STUDIES ON THE AVIAN NERVOUS SYSTEM

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## A B S T R A C T

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The Nauta-Gygax technique for the demonstration of degenerating axons has been applied to a study of projections of the cingulate gyrus, presubiculum and entorhinal area. Projections of these areas and inter-relations between them are described and the possible significance of such findings are discussed.

Progress in the investigation of the avian nervous system is reported with specific reference to ascending spinal projections. Particularly noteworthy was the demonstration for the first time of direct spino-thalamic connections.

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## I. INTRODUCTION:

The goal of the current investigative efforts was to obtain further information on hippocampal discharge pathways, and the projections of associated areas in intimate functional relationship to the hippocampus. During the past year investigations were directed towards the specific projections of the entorhinal area, presubiculum, and caudal cingulate gyrus. Each of these areas will be discussed separately. One of the most severe limitations of research on the above mentioned regions is their inaccessability and the resultant difficulty of placing discrete lesions in these areas without excessive involvement of adjacent areas. Such caution is especially necessary in anatomical studies using the very sensitive Nauta technique for degenerating axons. Specific features of the gross anatomical structure of the brain of the cat made this a most desirable experimental animal.

## II. PROGRESS:

### a. Entorhinal Area

It was possible to make lesions in the entorhinal area by means of an electrode placed over the tentorium cerebelli, extradurally, and advanced to the entorhinal area. Following such lesions the animals were allowed to survive 10-14 days and then studied by means of the Nauta technique. Such lesions resulted in degeneration of a distinct sub-ventricular bundle which merged with the external capsule and could be followed to termination in the lateral amygdaloid nucleus and, to a lesser degree, in the periamygdaloid cortex. A dense pattern of degeneration could be seen in the alveus and the molecular layers of the

fascia dentata and cornu ammonis and the hippocampal commissure. On rare occasion there appeared to be fibers entering the anterior commissure perhaps destined for the contralateral E.A., as suggested by Brodal. It was not possible to establish the existence of previously described projections (Adey, et al, 1956) to the stria medullaris or the tegmentum. Though one must consider the possibility of species differences (the above mentioned work was performed on the marsupial Phalanger) it must be pointed out that the Nauta technique is exquisitely sensitive to any secondary damage to the central nervous system. All projections to the tegmentum that were found were only seen when there was associated damage to the adjoining occipital cortex. However, the possibility does exist that further study may demonstrate such connections which may account for the reported substantiation of such projections by electrophysiologic methods.

#### Significance of this research

The clear cut demonstration of projections from the entorhinal area to the lateral amygdaloid nucleus is of great interest. Though a functional relationship had long been suspected on the basis of strychnine neuronography, this technique has long since been abandoned because of the often capricious nature of results obtained with it. More recent evidence, however, has given good cause to once again intimate the possibility of direct connections between these two structures. Mason and co-workers have consistently shown prolonged decrease in blood levels of 17-OH- corticosteroids, of long latency of onset, following stimulation of the hippocampus, whilst stimulation of the lateral amygdaloid nucleus resulted in elevation of these hormones.

The demonstration of direct connections between these two regions of the central nervous system provides a possible anatomical basis for such reciprocating phenomena. Amongst the possible underlying mechanism, that may account for the physiological findings, one must consider:

1. such connections arising in the hippocampus may mediate their long-lasting, profound depression of blood steroid levels by means of the forniceal projections directly inhibiting those hypothalamic areas concerned with control of pituitary release of ACTH, while those fibers followed to the amygdala represent information communicated to the amygdala of hippocampal activity;
2. the long-latency, prolonged response of depression of blood steroids may reflect a direct suppression of that portion of the amygdala concerned with control of these functions.

b. Presubiculum

Lesions of the presubiculum were found to give rise to degeneration of the fornix longus, which could be followed to termination in the septum, thalamic parataenial nucleus, lateral hypothalamus, medial mammillary body (pars lateralis), and the ventral tegmental area of Tsai. Other projections could be followed to the caudal cingulate gyrus, cingulum and entorhinal area, as well as to the hippocampus proper. The evidence was only suggestive that the projections to the molecular layer of the fascia dentata was denser in these cases than in those with lesions of the entorhinal area. That some of the fibers of the entorhinal area destined for the hippocampus course through the presubiculum, however, poses severe limitations on our ability to clearly delineate possible fine differences in the projection of these two cortical areas.

The above cited projections of the presubiculum thus provide three assured efferent paths. One via the hippocampus, another via the cingulate and cingulum bundle and the third by means of the fornix dorsalis. The nature of the relationship between the latter two, however, will require further investigation. It has long been recognized that fibers of the cingulum bundle traverse the corpus callosum and enter the fornix longus. The possibility exists, however, that these fibers actually originate in the presubiculum or subiculum, and are, in the course of phylogeny and with the development of the corpus callosum, simply separated from the fornix dorsalis, and penetrate the corpus callosum to rejoin it at more frontal levels. It has not yet been possible to selectively destroy all of the presubiculum and subsequently observe total degeneration of the fornix dorsalis.

#### Significance of these findings

The above findings demonstrate the existence of pathways which provide a means of generalization of hippocampal discharges to such diverse regions as the entorhinal area (and thereby, possibly the amygdala), cingulate cortex, septum, and thalamus and may lead to an understanding of the manner of spread and the nature of temporal lobe seizure discharges.

Of note, in all our findings was the distinct differences of projection to the dorsal vs. the ventral hippocampus. This reflects more than an inability to "totally" ablate the cortical areas in question. We were consistently able to produce profound degeneration in the dorsal hippocampus, while the more rostral reaches of the ventral hippocampus were always free of such degeneration. This finding is consistent with



many of the suggestions voiced on the basis of physiological experimentation, and supports, what until this time has been only suspected, that the hippocampus is not single uniform structure of homogeneous input and output.

#### c. Posterior Cingulate Gyrus

The posterior cingulate gyrus has been found to project profusely to the length of the cingulate gyrus, infra-limbic cortex, presubiculum, and minimally to the entorhinal area. Subcortical connections include those to the dorsal portions of the fornix dorsalis, thence to the septum, parataenial nucleus of the thalamus, anterior thalamic nuclei, caudo-lateral hypothalamus, pars lateralis of the medial mammillary nucleus, posterior hypothalamus and the ventral tagmental area of Tsai. Dense projections to the antero-ventral and lateral dorsal nuclei of the thalamus were noted with sparse numbers of fibers seen in the antero-dorsal nucleus of the thalamus. Capsular fibers were followed to termination in the Zona Incerta and medial pontine nuclei. Degeneration in a well localized region of the caudate nucleus was also consistently noted. Investigations of the projections of the anterior and middle cingulate gyrus are still in progress.

The above findings clearly demonstrate the relationship of the posterior cingulate gyrus to the anterior cingulate gyrus, but also provides evidence for intimate connections between the caudal regions of the cingulate gyrus and the infra-limbic cortex. Much of this latter zone immediately borders on the frontal lobe and may provide a means for limbic modulation of frontal lobe function. Taken in conjunction with recent findings of projections of the frontal lobe onto the cingulate

gyrus (Nauta, 1962), this suggests a mutually interacting system of frontal -limbic, limbic-frontal connections.

#### Studies on the Avian Nervous System

Little work has been done for almost a half century on the avian nervous system using experimental anatomical techniques. The importance of an understanding of the organization of the avian nervous system takes on increasing significance in light of the extensive investigations of the ethologists in England and Germany of the behaviour patterns of birds. Few contributions to our understanding of the avian CNS have appeared since the extensive summary found in Kappers, Huber and Crosby's monumental work. The predominant proportion of reports referred to in this latter work were done on normal material, with the exception of the studies of Wallenberg, using the Marchi techniques for degenerating axons. At present it is generally accepted that the Nauta technique for degenerating axons is a more dependable, sensitive and reliable technique than the Marchi, and it appeared worthwhile to apply the Nauta technique to this material.

In view of the controversy regarding the existence of spino-thalamic connections in infra-mammalian animals, attention was first directed towards a study of ascending projections from the spinal cord in the pigeon.

Hemisectons of the spinal cord of pigeons were made under direct vision at C12-14. The animals were sacrificed 7-14 days post-operation and the brains studied for ascending pathways using the Nauta technique for degenerating axons. Fibers could be followed in continuity to termination in the following regions (all terminations were ipsilateral with only few exceptions):

MEDULLA-PONS - Nuclei cuneatus and gracilis; caudal pole of the inferior olive; commissural nucleus of the vagus-solitary complex (nucleus infima); nucleus of the tractus solitarius; medial and lateral portions of the medial reticular nucleus (of Cajal), found in the ventro-lateral to medial zones; the raphe and paramedian nuclei; cerebellar cortex via distinct dorsal and ventral spino-cerebellar tracts.

TECTUM-MESENCEPHALON - Dense terminations in the lateral reticular nuclei to the level of the interpeduncular nucleus, with a diffuse spray of degenerating axons seen throughout the reticular formation and central grey substance of the mesencephalon. Dorsolaterally arching fibers could be followed to termination in the nucleus mesencephalicus lateralis, pars dorsalis, though completely sparing the central core of it corresponding to the torus semicircularis. The region of termination is possibly homologous to the stratum profundum of the superior colliculus of mammals. Other fibers could be traced to the lateral optic nucleus of Craigie, the stratum lemnisci of the tectum proper, the pretectal and the subpretectal nuclei.

THALAMUS - Degenerating axons could be seen penetrating the tectal and posterior commissures and entering the thalamus to terminate diffusely in the ventral portions of the anterior and posterior dorsolateral nuclei of the thalamus. Occasional fibers could be seen in the dorso-medial nucleus of the thalamus. No degenerating axons could be clearly identified in the "ventral" thalamic nuclei; e.g. nucleus rotundus, ovoidalis, etc.

### Significance of this research

As noted, the terminations in the thalamus were seen dorsal to the medial thalamic sulcus, whilst no degeneration could be discerned in the ventral complex of nuclei. This suggests that the previous statements regarding homologies of the reptilian and avian nervous system to that of mammals may be invalid. Such studies are leading to a newer understanding of the nature of thalamic evolution. Spino-thalamic projections may also reflect the widely accepted notion that mammals and birds both arose in evolution from some intermediate form of higher reptile, now extinct. This postulated form may have been the first to develop such direct connections which might have proven necessary in the more active, wider ranging life of homoiothermic animals.

Work in preparation shall extend to a study of the projections of the cerebellum, optic tectum, hippocampal cortex, and striatal structures in the bird.

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